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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/648,816 | 08/26/2003 | Nicholas Van Bruggen | 11669.0113USC1 | 5367 |

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| EXAMINER | |
|---|---|
| HOLLERAN, ANNE L | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1643 | |

DATE MAILED: 06/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/648,816 | VAN BRUGGEN ET AL. | |
| | Examiner | Art Unit | |
| | Anne L. Holleran | 1643 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) 1-38 is/are pending in the application.

4a) Of the above claim(s) 7-11,15-18 and 23-26 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-6,12-14,19-22 and 27-38 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 9/05, 8/03.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

1. The preliminary amendment filed 12/08/2003 is acknowledged. Claims 30-38 were added. Claims 1-38 are pending.

### *Election/Restrictions*

2. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 7-10, 15-18 and 23-26, drawn to methods of treating edema comprising the administration of anti-VEGF antibodies, classified in class 424, subclass 130.1.

II. Claims 11-13, 19-21, 27-29 and 36-38, drawn to methods of treating edema comprising the administration of VEGF receptor fusion proteins, classified in class 424, subclass 192.1.

3. The inventions are distinct, each from the other, for the following reasons:

Claims 1-6, 14, 22 and 30-35 link inventions I-II. The restriction requirement between the linked inventions is subject to the nonallowance of the linking claims, claims 1-6, 14, 22 and 30-35. Upon the allowance of the linking claims, the restriction requirement as to the linked inventions shall be withdrawn and any claims depending from or otherwise including all the limitations of the allowable linking claims will be entitled to examination in the instant application. Applicant is advised that if any such claims depending from or including all the limitations of the allowable linking claims are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional

statutory and/or nonstatutory double patenting rejections over the claims in the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. *In re Ziegler*, 44 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

4. Inventions I and II are directed to related inventions. The related inventions are distinct if the inventions as claimed do not overlap in scope, i.e., are mutually exclusive; the inventions as claimed are not obvious variants; and the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect. See MPEP § 806.05(j). In the instant case, the methods of group I require the use of anti-VEGF antibodies, which are distinct products from the products used in the methods of group II, which require the use of VEGF receptor fusion proteins. Thus, the methods of group I and group II have a materially different design because the methods use materially different and distinct products.

Because these inventions are independent or distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

5. During a telephone conversation with Katherine Kowalchyk on June 20, 2006 a provisional election was made without traverse to prosecute the invention of group II, claims 11-13, 19-21, 27-29 and 36-38. Affirmation of this election must be made by applicant in replying

to this Office action. Claims 7-10, 15-18 and 23-26 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

6. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

7. Claims 1-38 are pending. Claims 7-10, 15-18 and 23-26, drawn to non-elected inventions, are with withdrawn from consideration.

Claims 1-6, 14, 22, 30-35 (linking claims) and claims 11-13, 19-21, 27-29 and 36-38 are examined on the merits.

***Claim Objections***

8. Claims 32-34 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 32 recites that the non-neoplastic condition comprises stroke, and depends from claim 31, which recites a Markush group listing non-neoplastic conditions, where "stroke" is not listed.

***Claim Rejections - 35 USC § 112***

9. Claim 31 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis for this rejection is that claim 31 introduces new matter into the specification because some of the conditions listed in the claim are not associated with the condition of cerebral edema in the specification, nor can be readily envisioned by one of skill in the art as conditions associated with cerebral edema.

Claim 31 was introduced by preliminary amendment. Applicants indicate support for the new claims is found in the specification at pages 23-24. The listing of conditions in claim 31 is not associated with cerebral edema in the specification, but is instead associated with edema. Therefore, literal support for all of the conditions is not found in the specification. However, for some of the conditions, such as "head injury, spinal cord injury, cerebral malaria, birth asphyxia, glutamate toxicity, encephalopathy and hypoxia, one of skill in the art would readily envision that these conditions are associated with cerebral edema. To the extent claim 31 lists other conditions, support is lacking and it appears that claim 31 introduces new matter into the specification.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

10. Claim 1 is rejected under 35 U.S.C. 102(e) as being anticipated by either Jirousek (U.S. 6,093,740; issued July 25, 2000; effective filing date Apr. 30, 1997) or Aiello (U.S. 6,114,320; issued Sep. 5, 2000; effective filing May 1, 1996).

Claim 1 is drawn to treating a mammal having edema comprising administering to said mammal an effective amount of a hVEGF antagonist. The specification teaches that VEGF antagonists "inhibit, sequester or neutralize the mitogenic, angiogneic, vascular permeability or other biological activity of hVEGF" (page 4, line 9-10).

Jirousek teaches treating dermal edema due to increased vascular permeability associated with VPF/VEGF comprising administering a $\beta$-isozyme selective PKC inhibitor, (S)-3,4-[N,N'-1,1'-((2'ethoxy)-3'(O)-4'-(N,N-dimethylamino)-butane)-bis-(3,3'-indolyl)]-1(H)-pyrrole-2,5-dione (see abstract and column 2, line 49 – column 3, line 2; column 6, line 62 - column 7, line 3; claim 1). Thus, Jirousek teaches a method that is the same as that claimed.

Aiello teaches treating macular edema with (S)-3,4-[N,N'-1,1'-((2'ethoxy)-3'(O)-4'-(N,N-dimethylamino)-butane)-bis-(3,3'-indolyl)]-1(H)-pyrrole-2,5-dione (see abstract, and column 2, line 41 – column 3, line 30; claim 12). Thus, Aiello teaches a method that is the same as that claimed.

11. Claims 1 and 11-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Aiello-II (Aiello, L.P., et al, Proceedings of the National Academy of Sciences. USA, 92: 10457-10461, 1995) as evidenced by Aiello (supra) as evidenced by Aiello (supra).

Included within the scope of claim 1 and claims 11-13 is the treatment of edema comprising the administration of an hVEGF receptor fusion protein.

Aiello-II teaches the use of human flt-IgG fusion proteins to suppress retinal neovascularization in vivo (see abstract and page 10459, Figure 3). Aiello-II teaches the flt-IgG fusion protein can reduce the ischemia-induced retinal neovascularization in vivo (see page 10460, 1st column) and that the mouse model used exhibits the EGF elevation and increase in vascular permeability observed in proliferative diabetic retinopathy and other ischemic retinal disorders. Thus, inherent in the method of Aiello-II is the treatment of edema by the administration of flt-IgG fusion receptors. This inherency is supportd by teachings of Aiello (supra), which teaches that capillary permeability is affected by VEGF, and that ischemia stimulate the synthesis and secretion of growth factors such as VEGF in retinal pericytes, endothelial cells, the retinal pigment epithelium, glial cells and possibly other cell types and subsequently leads to retinal neovascularization and increased capillary permeability (see col. 9, lines 17-51).

Therefore, Aiello-II teaches a method that is the same as that claimed.

12. Claims 1-5, 11-13, 22 and 27-29 are rejected under 35 U.S.C. 102(b) as being anticipated by Ferrara (WO 94/10202; published 11 May 1994; cited in the IDS).

The claimed method are drawn to methods of treating edema, or cerebral edema, or edema associated with neoplastic disease, such as a brain tumor, comprising the administration of hVEGF antagonists, where the hVEGF antagonists may be hVEGF receptor fusion proteins.

Ferrara teaches methods of treatment comprising administering hVEGF antagonists, where the hVEGF antagonist may be a flt-IgG fusion protein (see page 22, lines 10-33; claim 30; apge 2, line 29-page 3, line 4). Ferrara also teaches combination therapy (see page 17, lines 15-28). Thus, Ferrara teaches methods that are the same as that claimed, because the active step of the claimed methods are the same as the active step of the methods taught by Ferrara. Furthermore, it appears that Ferrara appreciated that hVEGF antagonists would be useful in the treatment of diseases or disorder characterized by undesirable vascular permeability, such as edema associated with a brain tumor. Thus, Ferrara teaches methods that are the same as that claimed.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 1, 6, 14-21 and 30-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ferrara (supra) in view of Aiello (supra, U.S. Patent 6,114,320).

The claimed inventions include within their scope methods of treating cerebral edema, or stroke, where the cerebral edema is due to a non-neoplastic condition such as stroke, which may be ischemic stroke.

Ferrara teaches methods of treating diseases or disorders associated with edema, but fails to specifically identify disorders such as the non-neoplastic condition of ischemic stroke. However, Aiello teaches that ischemia plays a role in the development of vascular permeability because ischemia stimulates the synthesis and secretion of growth factors such as VEGF in retinal pericytes, endothelial cells, the retinal pigment epithelium, glial cells and possibly other cell types and subsequently leads to retinal neovascularization and increased capillary permeability. Therefore, it would have been prima facie obvious to one of ordinary skill in the

art at the time the invention was made to have used the method of Ferrara to treat cerebral edema due to non-neoplastic conditions such as ischemic stroke. One would have been motivated to have used Ferrara's method because Ferrara's method targets VEGF, which is taught by Aiello to be induced by conditions such as hypoxia.

***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne Holleran, whose telephone number is (571) 272-0833. The examiner can normally be reached on Monday through Friday from 9:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached on (571) 272-0832. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Official Fax number for Group 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Anne L. Holleran
Patent Examiner
June 26, 2006

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SUPERVISORY PATENT EXAMINER